

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: JUVÉDERM VOLBELLA[®] XC

Device Procode: LMH

Applicant's Name and Address: Allergan
2525 Dupont Drive
Irvine, CA 92612

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110033/S018

Date of FDA Notice of Approval: 5/31/2016

Priority Review: No

Expedited Access Pathway (EAP): No

The original PMA for JUVÉDERM VOLUMA XC (P110033) was approved on 10/22/2013 and is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the midface in adults over the age of 21. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. JUVÉDERM VOLBELLA[®] XC is being submitted as a panel-track supplement (P110033/S018) to the JUVÉDERM VOLUMA XC PMA, P110033, to request changes in design or performance of the device, and a new indication for use of the device. The current supplement was submitted for JUVÉDERM VOLBELLA[®] XC for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21.

II. INDICATIONS FOR USE

JUVÉDERM VOLBELLA[®] XC injectable gel is indicated for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21.

III. CONTRAINDICATIONS

- JUVÉDERM VOLBELLA[®] XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies
- JUVÉDERM VOLBELLA[®] XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material

- JUVÉDERM VOLBELLA[®] XC contains lidocaine and is contraindicated for patients with a history of allergies to such material

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the JUVÉDERM VOLBELLA[®] XC labeling.

V. DEVICE DESCRIPTION

JUVÉDERM VOLBELLA[®] XC injectable gel is a sterile, biodegradable, nonpyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of crosslinked hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, formulated to a concentration of 15 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for lip augmentation and for correction of perioral rhytids. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

Alternative therapies include autologous fat grafting, surgical facelift, and other soft tissue fillers approved by FDA for lip augmentation.

Fat grafting is similar in result and usually requires multiple sessions. Fat grafting requires an invasive procedure to remove fat from the body (such as lipoplasty). Risks of fat grafting include donor site morbidity, graft resorption, fat necrosis, oil cyst, and uneven result.

Surgical facelift is not directly comparable, but can decrease an aged look without providing additional volume. Facelift is a surgical procedure and carries the risks typically associated with a surgical procedure requiring general anesthesia and a prolonged recovery with scarring.

VII. MARKETING HISTORY

JUVÉDERM VOLBELLA[®] XC received the CE Mark on October 7, 2011, under the name JUVÉDERM VOLBELLA with Lidocaine. In addition to being marketed throughout Europe, JUVÉDERM VOLBELLA with Lidocaine is currently marketed globally, including Australia, Canada, Brazil, Russia, Ukraine, Mexico, Korea, Taiwan, and Singapore.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Potential adverse effects (e.g., complications) associated with the use of the device, as well as for other devices in the same category, as reported in the clinical study, include tenderness, swelling, firmness (induration), lumps/bumps (mass), bruising, pain, redness, discoloration, and itching.

The following reported adverse events were received from postmarket surveillance of the use of JUVÉDERM VOLBELLA® XC for lip augmentation outside the United States and were not observed in the clinical study. These adverse events, with a frequency of 5 or more events, are listed in order of prevalence: inflammatory reaction, loss/lack of correction, hematoma, allergic reaction, infection, paresthesia, herpes, migration, angioedema, and necrosis.

In addition, two reports of blurry vision after injection into the highly vascularized periorbital area were received from postmarket surveillance for JUVÉDERM VOLBELLA® XC used outside of the United States. Reported treatment included anti-inflammatories. The outcomes for these two reports were either ongoing or unknown at time of last contact.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Physical and Chemical Characterization

JUVÉDERM VOLBELLA® XC has been extensively tested and characterized through physical and chemical analyses (Table 1). Degradation assays were also performed to ensure that JUVÉDERM VOLBELLA® XC naturally degrades in the body during its clinical lifespan.

Table 1: Summary of Key Bench Testing on JUVÉDERM VOLBELLA® XC

Test	Purpose	Results
NaHA Concentration (mg/g)	Ensures HA concentration meets specification	Passed
Lidocaine Concentration (%w/w)	Ensures lidocaine concentration meets specification	Passed
pH	Ensures pH meets specification	Passed
Osmolarity (mOsmol/Kg)	Ensures osmolarity meets specification	Passed
Extrusion Force (N)	Ensures extrusion force meets specification	Passed
Residual Crosslinker (ppm)	Ensures residual crosslinker meets specifications	Passed
Endotoxin (EU/Syringe)	Ensures endotoxin meets specification	Passed

Filled syringes are sterilized using a validated moist heat process in a pressurized autoclave. The sterilization cycle is validated according to ISO 17665-1 sterilization standard. The validated sterilization cycle provides a minimum Sterility Assurance Level (SAL) of 10^{-6} .

Stability data have been collected through 36 months at 25°C/60% relative humidity, through 12 months at 30°C/65% relative humidity, and through 6 months at 40°C/75% relative humidity. At each time point, product was evaluated for conformance with microbiological, physical, chemical, lidocaine HCl potency, and lidocaine-related degradants. Conformance with all specifications was confirmed.

Biocompatibility Testing

JUVÉDERM VOLBELLA® XC was evaluated with in vitro and in vivo biocompatibility studies appropriate for devices in contact with tissue for greater than 30 days. The results of the tests are summarized in Table 2 below. The biocompatibility studies were performed in accordance with the Federal Good Laboratory Practices Regulations (21 CFR § 58), ISO 10993 and FDA’s Blue Book memorandum G95-1 “Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.”

Table 2: Summary of Biocompatibility Testing on JUVÉDERM VOLBELLA® XC

Test	Method	ISO standard	Results
Cytotoxicity	Agar overlay	10993-5	Non-cytotoxic
Sensitization	Guinea pig maximization test	10993-10	Non-sensitizing
Intracutaneous reactivity	72 hours in rabbit	10993-10	Non-irritant
Intracutaneous reactivity	14 days in rabbits	10993-10	No acceptance criteria; slight irritant microscopically
Acute Systemic Toxicity	Intraperitoneal injection in mice	10993-11	Not systemically toxic
Subchronic Toxicity (13 Weeks)	Intradermal injection in rats	10993-11	Non-toxic
Muscle Implantation (4 and 12 Weeks)	In rabbits	10993-6	Non-irritant
Subcutaneous Implantation (4 and 12 weeks)	In rats	10993-6	Not causing local skin reaction macroscopically; slight irritant microscopically
Pyrogenicity	Rabbit pyrogen study	USP <151>	Non-pyrogenic
Genotoxicity	Bacterial Reverse Mutation, Micronucleus, and Chromosomal Aberration	10993-3	Non-genotoxic Non-mutagenic

Carcinogenicity risks: The excess cancer risks for JUVÉDERM VOLBELLA® XC range from 6.1×10^{-5} to 1.6×10^{-8} from lifetime exposure to residual BDDE based on a linear extrapolation method and a dose-response model. The excess cancer risks for JUVÉDERM VOLBELLA® XC are in the same range of acceptable cancer risks as other previously approved dermal filler products.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness for JUVÉDERM VOLBELLA® XC for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21 in the US under IDE # G130054. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between November 25, 2013 and April 23, 2015. The database for this Panel Track Supplement reflected data collected through July 21, 2015 and included 224 subjects who were randomized and underwent treatment with either JUVÉDERM VOLBELLA® XC (N = 168) or control (N = 56) at the outset of the study. The control treatment was Restylane-L which is a legally marketed alternative with similar indications for use. There were 13 investigational sites.

The study was a prospective, double-blind, randomized, controlled, multicenter clinical study of subjects seeking lip augmentation and correction of perioral rhytids. Subjects meeting inclusion/exclusion criteria were randomized 3:1 to treatment with either JUVÉDERM VOLBELLA® XC or control.

1. Key Clinical Inclusion and Exclusion Criteria

Inclusion criteria:

- 22 years of age or older
- Had a score of Minimal, Mild, or Moderate on the LFS2, as agreed upon by the Treating and Evaluating Investigators, and desired at least 1-point improvement in overall LFS2 score
OR
had Fitzpatrick skin phototype V or VI and had an overall lip fullness score of Marked or Very Marked on the LFS2, as agreed upon by the Treating and Evaluating Investigators, and desired treatment to the vermilion body of 1 or both lips
- For treatment of perioral lines, had a POLSS score of Severe or Moderate as agreed upon by the Treating and Evaluating Investigators (subjects who met all other criteria were eligible for treatment in the vermilion body, oral commissures, vermilion border, Cupid's bow, and philtral columns)

Exclusion criteria:

- Had dentures or any device covering all or part of the upper palate, and/or severe malocclusion or dentofacial or maxillofacial deformities as judged by the Treating Investigator
- Had received permanent facial implants (e.g., polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck, or was planning to be implanted with any of these products during the study
- Had undergone semipermanent dermal filler treatment (e.g., calcium hydroxylapatite, poly-L-lactic acid) in the lower face (below the orbital rim) within 24 months before enrollment or was planning to undergo such treatment during the study
- Had undergone temporary dermal filler treatment (e.g., hyaluronic acid or collagen) in the lower face (below the orbital rim) within 12 months before enrollment or was planning to undergo such treatment during the study
- Had undergone facial tissue augmentation with fat injections, botulinum toxin injections in the lower face (below the orbital rim), mesotherapy, or cosmetic procedures in the face or neck (e.g., face-lift, laser, photo-modulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, or other ablative procedures) within 6 months before enrollment or was planning to undergo any of these procedures during the study
- Had used any lip plumping products within 10 days before enrollment or was planning to use such products during the study (study treatment was able to be delayed as necessary to accommodate this 10-day washout period)
- Had begun using any over-the-counter or prescription, oral or topical, anti-wrinkle products for the lips or around the mouth within 90 days before enrollment or was planning to begin using such products during the study (subjects who had been on a regimen of such products for at least 90 days were eligible for the study if they intended to continue their regimen throughout the study)
- Was on an ongoing regimen of anti-coagulation therapy (e.g., warfarin) or nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen) or other substances known to increase coagulation time (e.g., herbal supplements with garlic or ginkgo) within 10 days of undergoing study device injections (study treatment was able to be delayed as necessary to accommodate this 10-day washout period)
- Was on a concurrent regimen of lidocaine or structurally related local anesthetics (e.g., bupivacaine)
- Had a history of anaphylaxis, atopy, or allergy to lidocaine, hyaluronic acid products, or Streptococcal protein, or was planning to undergo desensitization therapy during the study
- Had an active inflammation, infection, cancerous or precancerous lesion, or unhealed wound in the mouth area
- Had porphyria
- Had impaired cardiac conduction, severely impaired hepatic function, or severe renal dysfunction

- Had any uncontrolled disease
- Had severe cardiovascular disease
- Females who were pregnant, nursing, or planning a pregnancy

2. Follow-up Schedule

In the pivotal study, subjects were randomized and underwent treatment with either JUVÉDERM VOLBELLA[®] XC or control at the outset of the study. Treatment occurred at up to 2 visits (initial and optional touch-up) approximately 30 days apart. Subjects completed a safety diary for 30 days after each treatment and attended safety follow-up visits at 3 and 14 days after each treatment.

The follow-up period consisted of safety and effectiveness follow-up visits at 1, 3, 6, 9, and 12 months after the last treatment. Subjects were then eligible for a repeat treatment with JUVÉDERM VOLBELLA[®] XC, with post-treatment follow-up for 1 month after repeat treatment, at which time all subjects completed the study.

The Treating Investigator determined the appropriate volume of VOLBELLA[®] XC or control to inject at initial, touch-up, and repeat treatments based on his/her clinical experience. Subjects received VOLBELLA[®] XC or control injections based on the randomization assignment. The maximum volume allowed for each lip was 1.5 mL at each treatment. Additional product was permitted to be injected into the perioral area as long as the total injection volume for an individual subject for the initial and touch-up treatments combined did not exceed 6.0 mL, and the volume of VOLBELLA[®] XC for the repeat treatment did not exceed 6.0 mL.

3. Clinical Endpoints

With regards to safety: the safety of JUVÉDERM VOLBELLA[®] XC in the lips and perioral area was evaluated by the presence, location, frequency, severity, and duration of ISRs after each treatment (initial, touch-up, and repeat) and any AEs throughout the study. ISRs were assessed by a subject safety diary for 30 days after each treatment. ISRs lasting beyond the 30-day diaries were considered adverse events (AEs). AEs were also reported by the Evaluating Investigator at follow-up visits.

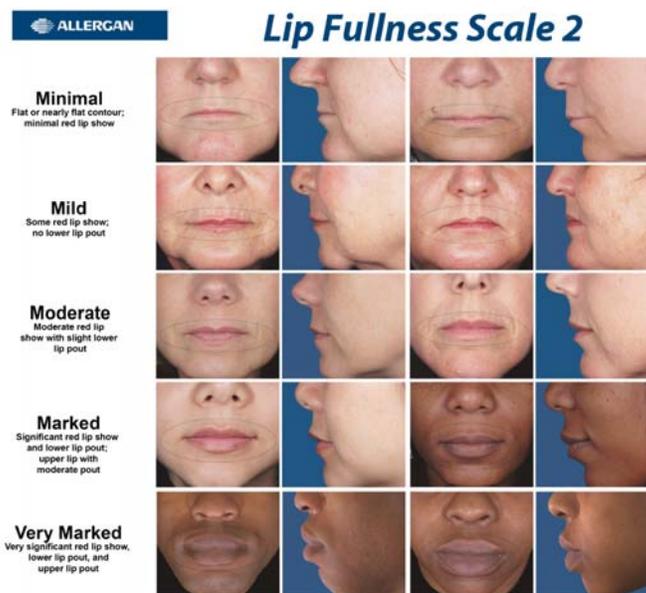
With regards to effectiveness: the primary effectiveness endpoint was the analysis of non-inferiority of JUVÉDERM VOLBELLA[®] XC relative to control in terms of change from baseline to month 3 in mean lip fullness based on Evaluating Investigator assessments using the validated 5-Point Lip Fullness Scale 2 (Table 3, Figure 1). Secondary endpoints included an analysis of the effectiveness of JUVÉDERM VOLBELLA[®] XC in the perioral region at month 3 based on the number and percent of responders on the POLSS (defined as a subjects demonstrating ≥ 1 -point improvement from baseline) and the mean and 95% confidence interval for the change from baseline to month 3 in scores for the *Satisfaction with Lips* module of the FACE-Q questionnaire.

With regard to success/failure criteria, the effectiveness of JUVÉDERM VOLBELLA® XC was demonstrated as noninferior to control if the lower limit of the 95% confidence interval for the difference in mean change in LFS2 from baseline to month 3 (JUVÉDERM VOLBELLA® XC minus control) was above the pre-specified noninferiority margin of -0.5.

Table 3: 5-Point Lip Fullness Scale 2 (LFS2)

Score	Grade	Description
4	Very Marked	Very significant red lip show, lower lip pout, and upper lip pout
3	Marked	Significant red lip show and lower lip pout
2	Moderate	Moderate red lip show with slight lower lip pout
1	Mild	Some red lip show; no lower lip pout
0	Minimal	Flat or nearly flat contour, minimal red lip show

Figure 1: Allergan Lip Fullness Scale 2



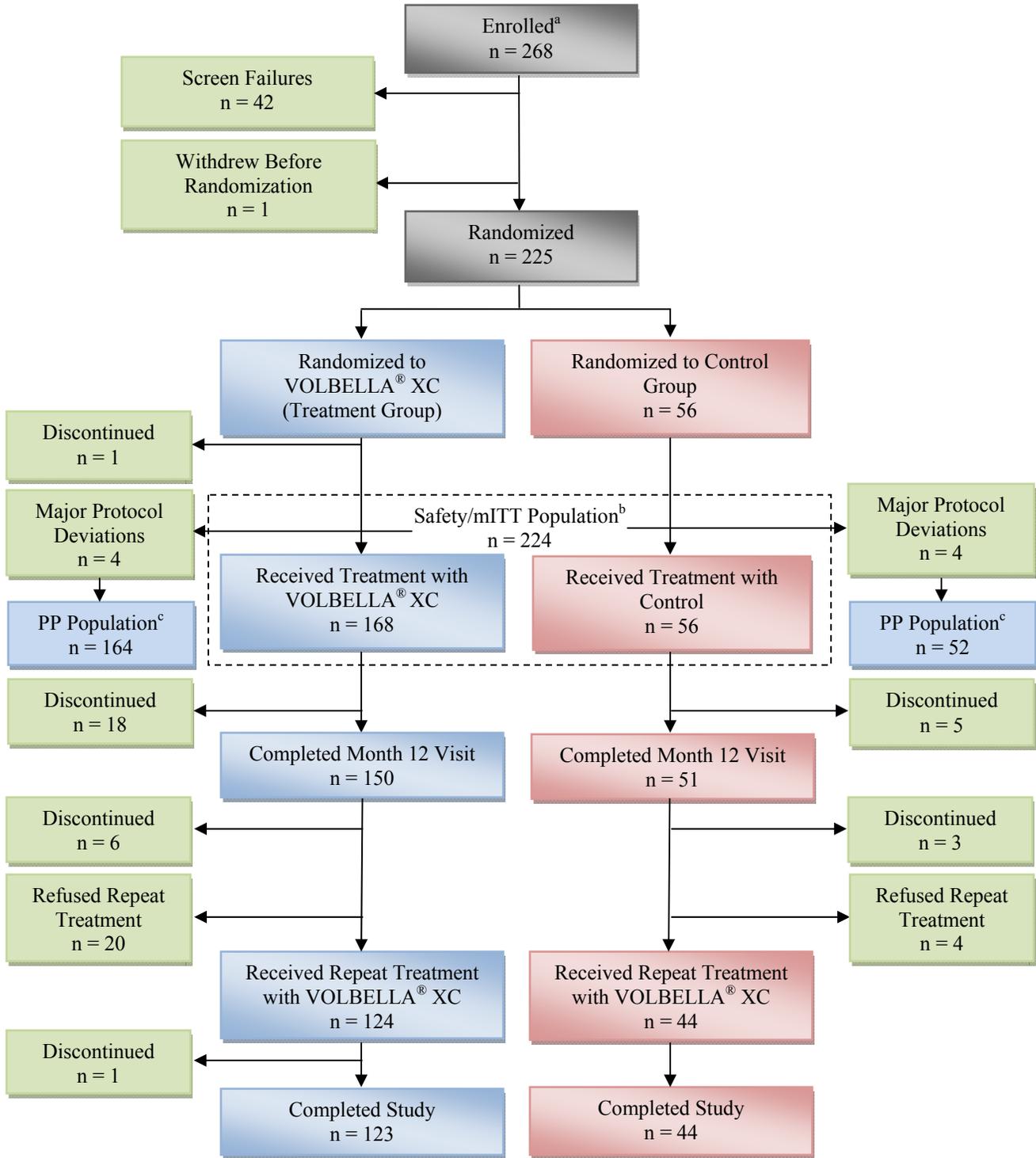
B. Accountability of PMA Cohort

The subject disposition is depicted as in Figure 2. A total of 268 subjects enrolled in the PMA study. After enrollment, 42 subjects (15.7%) were screen failures, and 1 subject (0.4%) withdrew consent prior to randomization resulting in 225 subjects (84.0%) randomized to treatment. Of the 225 randomized subjects, 169 were randomized to treatment with JUVÉDERM VOLBELLA® XC and 56 were randomized to treatment with control. One subject in the JUVÉDERM VOLBELLA® XC group (1/169, 0.6%) was randomized but discontinued before treatment. Thus, the mITT and safety populations included 224 subjects: 168 subjects in the JUVÉDERM VOLBELLA® XC group and 56 subjects in the control group. Of the 224 mITT subjects, 201 completed

follow-up through 12 months: 150 (88.8%) and 51 (91.1%) subjects in the JUVÉDERM VOLBELLA[®] XC and control groups, respectively.

Repeat treatment with JUVÉDERM VOLBELLA[®] XC was administered to 168 subjects in total: 124 (73.4%) and 44 (78.6%) subjects in the JUVÉDERM VOLBELLA[®] XC and control groups (based on original randomization), respectively. Of the 224 mITT subjects, 167 (74.6%) completed the study: 123 (73.2%) and 44 (78.6%) subjects in the JUVÉDERM VOLBELLA[®] XC and control groups, respectively. The reasons for early discontinuation in the JUVÉDERM VOLBELLA[®] XC group were refusal of repeat treatment (11.9%, 20/168), loss to follow-up (7.1%, 12/168), withdrew consent (4.8%, 8/168), other (1.8%, 3/168), AE (0.6%, 1/168), and protocol violations (0.6%, 1/168). The most common reason given for refusal of repeat treatment in the JUVÉDERM VOLBELLA[®] XC group was satisfaction with current lip fullness. In the control group, the reasons for early discontinuation were refusal of repeat treatment (7.1%, 4/56), loss to follow-up (7.1%, 4/56), withdrew consent (1.8%, 1/56), other (3.6%, 2/56), and AE (1.8%, 1/56).

Figure 2: Disposition of subjects



^a Enrolled population consists of all enrolled subjects screened for enrollment and recorded with screening log data. A subject is considered enrolled when s/he has signed the consent form.

^b The safety population consists of all subjects who received at least one study treatment. The modified intent-to-treat (mITT) population consists of all subjects who were randomized and received at least one study treatment.

^c The per-protocol (PP) population consists of all mITT subjects who do not have any significant protocol deviations that affect the primary effectiveness endpoint.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. Subject demographics and pretreatment characteristics of the JUVÉDERM VOLBELLA® XC and control groups are presented in Table 4.

Table 4: Subject Demographics and Pretreatment Characteristics (N = 224)

	JUVÉDERM VOLBELLA® XC	Control
	(N = 168)	(N = 56)
	% (n/N)	% (n/N)
Gender		
Female	97.6% (164/168)	94.6% (53/56)
Male	2.4% (4/168)	5.4% (3/56)
Age		
Median	53	55
Range	22-78	23-75
Race		
Caucasian	85.7% (144/168)	87.5% (49/56)
African-American	8.9% (15/168)	10.7% (6/56)
Asian	1.8% (3/168)	1.8% (1/56)
American Indian or Alaska Native	1.2% (2/168)	0% (0/56)
Other	2.4% (4/168)	0% (0/56)
Ethnicity		
Not Hispanic or Latino	92.9% (156/168)	91.1% (51/56)
Hispanic or Latino	7.1% (12/168)	8.9% (5/56)
Fitzpatrick Skin Type		
I	10.7% (18/168)	10.7% (6/56)
II	29.8% (50/168)	26.8% (15/56)
III	31.5% (53/168)	33.9% (19/56)
IV	15.5% (26/168)	16.1% (9/56)
V	6.5% (11/168)	5.4% (3/56)
VI	6.0% (10/168)	7.1% (4/56)
Baseline Overall Lip Fullness (LFS2) Score		
Very Marked	0% (0/168)	0% (0/56)
Marked	1.8% (3/168)	5.4% (3/56)
Moderate	35.1% (59/168)	26.8% (15/56)
Mild	43.5% (73/168)	48.2% (27/56)
Minimal	19.6% (33/168)	19.6% (11/56)

The median volume for initial and touch-up treatment combined was 2.6 mL (range 0.5 to 6.0 mL). The median volume for repeat treatment was 1.6 mL (range 0.3 to 4.0 mL). For each treatment, similar total volumes were used in each group.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 224 patients, etc. available for the 13 month evaluation. The key safety outcomes for this study are presented below in Tables 5 to 7. Adverse effects are reported in Tables 8 to 12.

Injection Site Responses

Injection site responses (ISRs) were assessed by a subject safety diary for 30 days after initial treatment, touch-up treatment (if performed), and repeat treatment. The severity and duration of all ISRs reported by > 5% of subjects who completed post-treatment diary forms after initial treatment are summarized in Table 5 and Table 6, respectively. Table 7 shows the severity and duration of all ISRs after repeat treatment with Juvéderm VOLBELLA[®] XC reported by > 5% of subjects.

Nearly all subjects (97.4%, 150/154 after initial treatment and 90.2%, 111/123 after repeat treatment) treated with Juvéderm VOLBELLA[®] XC reported at least 1 ISR. The most frequently reported ISRs after initial and repeat treatment were swelling (92.9%, 143/154, and 87.8%, 108/123, respectively), tenderness (89.6%, 138/154, and 83.7%, 103/123, respectively), firmness (89.0%, 137/154, and 80.5%, 99/123, respectively), and bruising (89.0%, 137/154, and 77.2%, 95/123, respectively). Other common ISRs were lumps/bumps (87.7%, 135/154), redness (83.1%, 128/154), and pain (80.5%, 124/154). Subjects reported the severity of their ISR after initial treatment as mild (14.7%, 22/150), moderate (45.3%, 68/150), or severe (40.0%, 60/150). Most ISRs lasted less than 2 weeks after initial (59.3%, 89/150) and repeat treatment (73.9%, 82/111), but 40.7% of the ISR lasted between 15-30 days of duration. The most common ISRs that lasted for 15 to 30 days after initial treatment were lumps/bumps (33.3%, 45/135), Dryness (25.0%, 2/8) and firmness (15.3%, 21/137). Similarly after repeat treatment, the most common ISRs lasting 15 to 30 days were lumps/bumps (22.4%, 22/98), firmness (13.1%, 13/99), and tenderness (3.9%, 4/103).

After repeat treatment with JUVÉDERM VOLBELLA[®] XC, Similar types of ISRs were reported after repeat treatment for subjects in the JUVÉDERM VOLBELLA[®] XC (90.2%, 111/123) and control group (90.9% [40/44]). Subjects in JUVÉDERM VOLBELLA[®] XC and control group reported the severity of their ISR after repeat treatment as mild (18.9%, 21/111, and 12.5%, 5/40, respectively), moderate (44.1%, 49/111, and 55.0%, 22/40, respectively), or severe (36.9%, 41/111, 32.5%, 13/40, respectively).

There were no significant differences in ISRs reported between JUVÉDERM VOLBELLA[®] XC and control. The incidence, severity, and duration of ISRs reported after the touch-up and repeat treatments were generally lower than those reported after initial treatment.

Table 5: Severity of Injection Site Responses after Initial Treatment^a Occurring in > 5% of Treated Subjects

Injection Site Response	JUVÉDERM VOLBELLA® XC				Control			
	Incidence (n/N ^b)	Severity ^c			Incidence (n/N ^a)	Severity ^c		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Any ISR	97.4% (150/154)	14.7% (22/150)	45.3% (68/150)	40.0% (60/150)	98.0% (50/51)	8.0% (4/50)	44.0% (22/50)	48.0% (24/50)
Swelling	92.9% (143/154)	23.1% (33/143)	49.7% (71/143)	27.3% (39/143)	98.0% (50/51)	16.0% (8/50)	46.0% (23/50)	38.0% (19/50)
Tenderness	89.6% (138/154)	53.6% (74/138)	32.6% (45/138)	13.8% (19/138)	92.2% (47/51)	23.4% (11/47)	66.0% (31/47)	10.6% (5/47)
Firmness	89.0% (137/154)	32.8% (45/137)	48.2% (66/137)	19.0% (26/137)	92.2% (47/51)	25.5% (12/47)	59.6% (28/47)	14.9% (7/47)
Bruising	89.0% (137/154)	35.0% (48/137)	40.9% (56/137)	24.1% (33/137)	90.2% (46/51)	30.4% (14/46)	47.8% (22/46)	21.7% (10/46)
Lumps/Bumps	87.7% (135/154)	43.0% (58/135)	42.2% (57/135)	14.8% (20/135)	90.2% (46/51)	30.4% (14/46)	52.2% (24/46)	17.4% (8/46)
Redness	83.1% (128/154)	47.7% (61/128)	39.1% (50/128)	13.3% (17/128)	88.2% (45/51)	40.0% (18/45)	44.4% (20/45)	15.6% (7/45)
Pain	80.5% (124/154)	58.9% (73/124)	30.6% (38/124)	10.5% (13/124)	92.2% (47/51)	42.6% (20/47)	46.8% (22/47)	10.6% (5/47)
Discoloration	41.6% (64/154)	54.7% (35/64)	34.4% (22/64)	10.9% (7/64)	49.0% (25/51)	40.0% (10/25)	36.0% (9/25)	24.0% (6/25)
Itching	30.5% (47/154)	76.6% (36/47)	17.0% (8/47)	6.4% (3/47)	37.3% (19/51)	63.2% (12/19)	36.8% (7/19)	0% (0/19)
Dryness	5.2% (8/154)	37.5% (3/8)	37.5% (3/8)	25.0% (2/8)	3.9% (2/51)	0% (0/2)	50% (1/2)	50% (1/2)

^a Does not include data after touch-up treatment

^b N denotes the number of subjects who recorded in the diaries after initial treatment

^c Maximum severity reported in the diary. Denominator for percentages by severity is the number of subjects with corresponding ISR

Table 6: Duration of Injection Site Responses after Initial Treatment^a Occurring in > 5% of Treated Subjects

Injection Site Response	JUVÉDERM VOLBELLA [®] XC					Control				
	Incidence (n/N ^b)	Duration ^c				Incidence (n/N ^a)	Duration ^c			
		1-3 Days	4-7 Days	8-14 Days	15-30 Days		1-3 Days	4-7 Days	8-14 Days	15-30 Days
Any ISR	97.4% (150/154)	9.3% (14/150)	30.0% (45/150)	20.0% (30/150)	40.7% (61/150)	98.0% (50/51)	6.0% (3/50)	44.0% (22/50)	8.0% (4/50)	42.0% (21/50)
Swelling	92.9% (143/154)	46.9% (67/143)	34.3% (49/143)	13.3% (19/143)	5.6% (8/143)	98.0% (50/51)	42.0% (21/50)	36.0% (18/50)	12.0% (6/50)	10.0% (5/50)
Tenderness	89.6% (138/154)	47.8% (66/138)	29.0% (40/138)	15.2% (21/138)	8.0% (11/138)	92.2% (47/51)	31.9% (15/47)	36.2% (17/47)	25.5% (12/47)	6.4% (3/47)
Firmness	89.0% (137/154)	39.4% (54/137)	27.0% (37/137)	18.2% (25/137)	15.3% (21/137)	92.2% (47/51)	29.8% (14/47)	40.4% (19/47)	10.6% (5/47)	19.1% (9/47)
Bruising	89.0% (137/154)	32.8% (45/137)	49.6% (68/137)	13.9% (19/137)	3.6% (5/137)	90.2% (46/51)	26.1% (12/46)	65.2% (30/46)	8.7% (4/46)	0% (0/46)
Lumps/Bumps	87.7% (135/154)	24.4% (33/135)	25.2% (34/135)	17.0% (23/135)	33.3% (45/135)	90.2% (46/51)	32.6% (15/46)	23.9% (11/46)	4.3% (2/46)	39.1% (18/46)
Redness	83.1% (128/154)	65.6% (84/128)	28.1% (36/128)	5.5% (7/128)	0.8% (1/128)	88.2% (45/51)	57.8% (26/45)	35.6% (16/45)	6.7% (3/45)	0% (0/45)
Pain	80.5% (124/154)	75.8% (94/124)	18.5% (23/124)	4.8% (6/124)	0.8% (1/124)	92.2% (47/51)	61.7% (29/47)	31.9% (15/47)	6.4% (3/47)	0% (0/47)
Discoloration	41.6% (64/154)	64.1% (41/64)	26.6% (17/64)	6.3% (4/64)	3.1% (2/64)	49.0% (25/51)	68.0% (17/25)	20.0% (5/25)	4.0% (1/45)	8.0% (2/25)
Itching	30.5% (47/154)	72.3% (34/47)	17.0% (8/47)	8.5% (4/47)	2.1% (1/47)	37.3% (19/51)	78.9% (15/19)	21.1% (4/19)	0% (0/19)	0% (0/19)
Dryness	5.2% (8/154)	37.5% (3/8)	0% (0/8)	37.5% (3/8)	25.0% (2/8)	3.9% (2/51)	0% (0/2)	50.0% (1/2)	0% (0/2)	50.0% (1/2)

^a Does not include data after touch-up treatment

^b N denotes the number of subjects who recorded in the diaries after initial treatment

^c Maximum reported successive occurrence of an ISR. Denominator for percentages by duration is the number of subjects with corresponding ISR

Table 7: Severity and Duration of Injection Site Responses after Repeat Treatment with JUVÉDERM VOLBELLA® XC Occurring in > 5% of Treated Subjects

Injection Site Response	Incidence (n/N ^a)	Severity ^b			Duration ^c			
		Mild	Moderate	Severe	1-3 Days	4-7 Days	8-14 Days	15-30 Days
Any ISR	90.2% (111/123)	18.9% (21/111)	44.1% (49/111)	36.9% (41/111)	18.0% (20/111)	30.6% (34/111)	25.2% (28/111)	26.1% (29/111)
Swelling	87.8% (108/123)	36.1% (39/108)	41.7% (45/108)	22.2% (24/108)	50.9% (55/108)	33.3% (36/108)	13.9% (15/108)	1.9% (2/108)
Tenderness	83.7% (103/123)	47.6% (49/103)	35.9% (37/103)	16.5% (17/103)	52.4% (54/103)	27.2% (28/103)	16.5% (17/103)	3.9% (4/103)
Firmness	80.5% (99/123)	39.4% (39/99)	39.4% (39/99)	21.2% (21/99)	39.4% (39/99)	22.2% (22/99)	25.3% (25/99)	13.1% (13/99)
Lumps/Bumps	79.7% (98/123)	41.8% (41/98)	39.8% (39/98)	18.4% (18/98)	39.8% (39/98)	22.4% (22/98)	15.3% (15/98)	22.4% (22/98)
Bruising	77.2% (95/123)	36.8% (35/95)	43.2% (41/95)	20.0% (19/95)	40.0% (38/95)	43.2% (41/95)	16.8% (16/95)	0.00% (0/95)
Pain	72.4% (89/123)	44.9% (40/89)	47.2% (42/89)	7.9% (7/89)	68.5% (61/89)	15.7% (14/89)	12.4% (11/89)	3.4% (3/89)
Redness	69.9% (86/123)	48.8% (42/86)	37.2% (32/86)	14.0% (12/86)	62.8% (54/86)	29.1% (25/85)	7.0% (6/86)	1.2% (1/86)
Discoloration	30.9% (38/123)	60.5% (23/38)	31.6% (12/38)	7.9% (3/38)	76.3% (29/38)	21.1% (8/38)	2.6% (1/38)	0.00% (0/38)
Itching	26.0% (32/123)	50.0% (16/32)	46.9% (15/32)	3.1% (1/32)	71.9% (23/32)	18.8% (6/32)	6.3% (2/32)	3.1% (1/32)

^a N denotes the number of subjects who recorded in the diaries after initial and repeat treatment with JUVÉDERM VOLBELLA® XC

^b Maximum severity reported in the diary.

^c Maximum reported successive occurrence of an ISR.

Adverse Events

Adverse events (AEs) were reported by Evaluating Investigators throughout the study: 104/168 (61.9%) of JUVÉDERM VOLBELLA® XC and 37/56 (66.1%) of control subjects experienced at least one treatment emergent adverse events, TEAEs (related and unrelated to the treatment). ISRs that lasted beyond the 30-day diaries were also considered AEs.

After initial treatment (or touch-up treatment, if performed), treatment-related AEs were reported in 50.0% (84/168) of subjects treated with JUVÉDERM VOLBELLA® XC and 51.8% (29/56) of subjects treated with control. All the treatment emergent adverse events with an incidence rate > 5% were treatment related. A summary of treatment-related AEs after initial/touch-up treatment is provided in Table 8. The severity and duration of treatment-related AEs reported by > 5% of subjects after initial treatment (or touch-up treatment) are summarized in Table 9 and Table 10.

Most subjects treated with JUVÉDERM VOLBELLA[®] XC experienced mild (42.3%, 71/168) or moderate (17.3%, 29/168) treatment-related AEs, only 1.2% (2/168) of subjects experienced severe treatment-related AE. Similar results were observed after treatment with control (41.1% [23/56], 23.2% [13/56], and 7.1% [4/56] of subjects experienced mild, moderate and severe AEs, respectively). Regardless of treatment group, the treatment-related AEs generally required no action to be taken and resolved without sequelae (49.4% [83/168] and 51.8% [29/56] of subjects in VOLBELLA[®] XC group and in control group, respectively).

Treatment-related TEAEs resolved within 7 days of onset for 22.0% (37/168) of subjects, 8-14 days for 11.3% (19/168) of subjects, 15-30 days for 12.5% (21/168) of subjects, and longer than 30 days for 30.4% (51/168) of subjects treated with JUVÉDERM VOLBELLA[®] XC. Treatment-related TEAEs with a duration of more than 180 days include: injection site mass (3.0%, 5/168 subjects); injection site erythema (1.2%, 2/168); injection site pain, injection site swelling, and wound (puncture marks on right and left sides of upper lip per investigator term) (each 0.6%, 1/168).

Table 3: Summary of Treatment-Related Adverse Events after Initial/Touch-up Treatment

	JUVÉDERM VOLBELLA® XC		Control	
	Subjects (N = 168)	Events (N = 345)	Subjects (N = 56)	Events (N = 111)
	n (%)	n (%)	n (%)	n (%)
Overall	84 (50.0)	345 (100)	29 (51.8)	111 (100)
At Injection Site				
Upper Lip	67 (39.9)	140 (40.6)	27 (48.2)	50 (45.0)
Lower Lip	60 (35.7)	133 (38.6)	22 (39.3)	47 (42.3)
Perioral Lines	21 (12.5)	27 (7.8)	5 (8.9)	7 (6.3)
Oral Commissures	22 (13.1)	40 (11.6)	5 (8.9)	7 (6.3)
Not at Injection Site	5 (3.0)	5 (1.4)	0 (0.0)	0 (0.0)
Duration				
≤ 7 Days	37 (22.0)	89 (25.8)	15 (26.8)	51 (45.9)
8-14 Days	19 (11.3)	47 (13.6)	7 (12.5)	11 (9.9)
15-30 Days	21 (12.5)	39 (11.3)	4 (7.1)	9 (8.1)
> 30 Days	51 (30.4)	167 (48.4)	15 (26.8)	36 (32.4)
Not yet Resolved ^a	3 (1.8)	3 (0.9)	1 (1.8)	4 (3.6)
Severity				
Mild	71 (42.3)	269 (78.0)	23 (41.1)	63 (56.8)
Moderate	29 (17.3)	71 (20.6)	13 (23.2)	34 (30.6)
Severe	2 (1.2)	5 (1.4)	4 (7.1)	14 (12.6)
Causality				
Device	58 (34.5)	205 (59.4)	19 (33.9)	42 (37.8)
Procedure	44 (26.2)	139 (40.3)	19 (33.9)	69 (62.2)
Unknown	1 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Outcome				
Resolved without sequelae	83 (49.4)	342 (99.1)	29 (51.8)	107 (96.4)
Ongoing ^a	3 (1.8)	3 (0.9)	1 (1.8)	4 (3.6)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment Required				
No	78 (46.4)	308 (89.3)	25 (44.6)	91 (82.0)
Medication	18 (10.7)	36 (10.4)	9 (16.1)	18 (16.2)
Procedure	1 (0.6)	1 (0.3)	1 (1.8)	2 (1.8)

^a The ongoing treatment-related AEs were ongoing at study exit. No additional information is available on the resolution of these AEs.

Table 4: Severity of Treatment-Related Adverse Events after Initial/Touch-Up Treatment Occurring in > 5% of Treated Subjects

Adverse Event	JUVÉDERM VOLBELLA® XC (N = 168)				Control (N = 56)			
	Subjects ^a	Mild ^a	Moderate ^a	Severe ^a	Subjects ^a	Mild ^a	Moderate ^a	Severe ^a
Injection Site Mass	32.1% (54/168)	26.8%	4.2%	1.2%	26.8% (15/56)	17.9%	5.4%	3.6%
Injection Site Bruising	17.9% (30/168)	10.7%	7.1%	0%	19.6% (11/56)	10.7%	8.9%	0%
Injection Site Pain	11.9% (20/168)	7.7%	4.2%	0%	21.4% (12/56)	8.9%	8.9%	3.6%
Injection Site Induration	8.9% (15/168)	7.7%	0.6%	0.6%	7.1% (4/56)	3.6%	3.6%	0%
Injection Site Swelling	8.3% (14/168)	4.8%	3.6%	0%	12.5% (7/56)	3.6%	3.6%	5.4%
Injection Site Dryness	4.2% (7/168)	3.0%	1.2%	0%	5.4% (3/56)	1.8%	3.6%	0%

^a The percentages are based on the number of subjects who received treatment with the corresponding product.

Table 5: Duration of Treatment-Related Adverse Events after Initial/Touch-Up Treatment Occurring in > 5% of Treated Subjects

Adverse Event	JUVÉDERM VOLBELLA® XC						Control					
	Events % (n/N ^a)	≤ 7 Days ^b %	8-14 Days ^b %	15-30 Days ^b %	> 30 Days ^b %	Not yet Resolved %	Events % (n/N ^a)	≤ 7 Days ^b %	8-14 Days ^b %	15-30 Days ^b %	> 30 Days ^b %	Not yet Resolved %
Injection Site Mass	29.0% (100/345)	5.0%	1.0%	15.0%	76.0%	3.0%	26.1% (29/111)	10.3%	3.4%	3.4%	69.0%	13.8%
Injection Site Bruising	15.9% (55/345)	52.7%	2.9%	14.5%	3.6%	0%	18.0% (20/111)	60.0%	30.0%	10.0%	0%	0%
Injection Site Pain	12.2% (42/345)	50.0%	9.5%	4.8%	35.7%	0%	18.9% (21/111)	85.7%	9.5%	0%	4.8%	0%
Induration Site Induration	12.5% (43/345)	0%	4.7%	0%	95.3%	0%	6.3% (7/111)	0%	0%	0%	100%	0%
Injection Site Swelling	9.3% (32/345)	43.8%	18.8%	6.3%	31.3%	0%	15.3% (17/111)	64.7%	0%	11.8%	23.5%	0%
Injection Site Dryness	3.8% (13/345)	0%	46.2%	0%	53.8%	0%	4.5% (5/111)	60.0%	0%	40.0%	0%	0%

^a N denotes the number of subjects who received treatment with the corresponding product.

^b The percentages by duration are based on the number of subjects with the corresponding treatment-related adverse event.

Treatment-related AEs after initial/touch-up treatment occurring in ≤ 5% of subjects included chapped lips, dizziness, dry lip, general physical condition abnormal, headache, lip disorder (lumps), lip injury, oral herpes, presyncope, wound, and injection site discoloration, edema, erythema, exfoliation, pruritus, reaction, discomfort, hyperaesthesia, nodule, papule, hypoaesthesia, laceration, and paraesthesia.

After initial/touch-up treatment, some AEs occurred weeks to months after the injection procedure. Treatment-related AEs with onset after 30 days were reported for 7 subjects in the JUVÉDERM VOLBELLA[®] XC group as follows:

- In 1 subject, mild injection site mass occurred between 30 to 60 days after initial/touch-up treatment. This AE required no treatment and resolved without sequelae.
- In 3 subjects, mild injection site nodules, edema, mass, and swelling occurred between 60 to 90 days after initial/touch-up treatment. The nodules, edema, and mass required no treatment and resolved without sequelae. The swelling was treated with acetaminophen and also resolved without sequelae.
- In 2 subjects, injection site swelling and lip disorder (lumps) occurred between 90 to 180 days after initial/touch-up treatment. The swelling was treated with doxycycline and resolved without sequelae. The lip disorder required no treatment and also resolved without sequelae.
- In 2 subjects, injection site mass occurred after 180 days. These AEs required no treatment and resolved without sequelae.

After repeat treatment with JUVÉDERM VOLBELLA[®] XC, treatment-related AEs were reported in 13.7% (17/124) and 15.9% (7/44) of subjects in the JUVÉDERM VOLBELLA[®] XC and control groups, respectively. A summary of treatment-related AEs after repeat treatment with JUVÉDERM VOLBELLA[®] XC by randomization group is provided in Table 11. The treatment-related AEs were similar between the two groups after repeat treatment. The severity and duration of AEs reported by > 5% of subjects after repeat treatment are summarized in Table 12. Similar types of treatment-related AEs were reported after repeat treatment, but with a lower incidence rate, severity, and duration compared to initial/touch-up treatment.

Treatment-related AEs after repeat treatment occurring in ≤ 5% of subjects included chapped lips, injection site bruising, edema, induration, and pain.

There were no treatment-related serious adverse events reported in the study.

Table 6: Summary of Treatment-Related Adverse Events after Repeat Treatment

	JUVÉDERM VOLBELLA® XC		Control*	
	Subjects	Events	Subjects	Events
	(N = 124) n (%)	(N = 46) n (%)	(N = 44) n (%)	(N = 10) n (%)
Overall	17 (13.7)	46 (100)	7 (15.9)	10 (100)
At Injection Site				
Upper Lip	12 (9.7)	16 (34.8)	6 (13.6)	6 (60.0)
Lower Lip	12 (9.7)	17 (37.0)	3 (6.8)	3 (30.0)
Perioral Lines	7 (5.6)	7 (15.2)	0 (0.0)	0 (0.0)
Oral Commissures	3 (2.4)	4 (8.7)	1 (2.3)	1 (10.0)
Not at Injection Site	1 (0.8)	2 (4.3)	0 (0.0)	0 (0.0)
Duration				
≤ 7 Days	7 (5.6)	12 (26.1)	0 (0.0)	0 (0.0)
8-14 Days	2 (1.6)	3 (6.5)	1 (2.3)	1 (10.0)
15-30 Days	3 (2.4)	4 (8.7)	1 (2.3)	1 (10.0)
> 30 Days	9 (7.3)	26 (56.5)	2 (4.5)	2 (20.0)
Not yet Resolved	1 (0.8)	1 (2.2)	4 (9.1)	6 (60.0)
Severity				
Mild	10 (8.1)	27 (58.7)	3 (6.8)	4 (40.0)
Moderate	9 (7.3)	18 (39.1)	3 (6.8)	5 (50.0)
Severe	1 (0.8)	1 (2.2)	1 (2.3)	1 (10.0)
Causality				
Device	8 (6.5)	18 (39.1)	3 (6.8)	5 (50.0)
Procedure	10 (8.1)	26 (56.5)	2 (4.5)	2 (20.0)
Unknown	1 (0.8)	2 (4.3)	2 (4.5)	3 (30.0)
Outcome				
Resolved without sequelae	16 (12.9)	45 (97.8)	4 (9.1)	4 (40.0)
Ongoing	1 (0.8)	1 (2.2)	4 (9.1)	6 (60.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment Required				
No	15 (12.1)	43 (93.5)	7 (15.9)	10 (100)
Medication	2 (1.6)	3 (6.5)	0 (0.0)	0 (0.0)

*denotes subjects who received initial treatment in control but repeat treatment with JUVÉDERM VOLBELLA® XC

Table 7: Severity and Duration of Treatment-Related Adverse Events after Repeat Treatment Occurring in > 5% of Treated Subjects

Adverse Event	JUVÉDERM VOLBELLA® XC									
	Subjects % (n/N)	Severity			Events % (n/N)	Duration				
		Mild ^a	Moderate ^a	Severe ^a		≤ 7 Days ^b	8-14 Days ^b	15-30 Days ^b	> 30 Days ^b	Not yet Resolved ^b
Injection Site Mass	7.3% (9/124)	5.6 %	0.8%	0.8%	32.6% (15/46)	0%	0%	13.3%	80.0%	6.7%

^a The percentages by severity are based on the number of subjects who received repeat treatment.

^b The percentages by duration are based on the number of events for the corresponding treatment-related adverse event.

Subgroup analyses

Subgroup analyses of ISRs and device-related AEs were performed by Fitzpatrick skin phototype (grouped as I/II, III/IV, and V/VI), age group (< 30, 30 to 50, 51 to 65, and > 65 years), volume injected (< or ≥ the median injected volume of 2.6 mL), and investigational site (Table 13). For ISRs after initial/touch-up treatment, there were no significant differences between the treatment and control groups for any subgroup in terms of overall ISR incidence or individual incidences. ISRs after repeat treatment were similar within each subgroup category. For device-related AEs after initial/touch-up treatment, no significant differences between the treatment and control groups were observed for any subgroup in terms of overall incidence of device-related AEs. Device-related AEs after repeat treatment were similar within each subgroup category.

Table 13: Incidence of Device-Related Adverse Events after Initial/Touch-up Treatment by Subgroup

	JUVÉDERM VOLBELLA® XC n/N (%)	Control n/N (%)
Fitzpatrick Skin Phototype		
I/II	42.6% (29/68)	42.9% (9/21)
III/IV	43.0% (34/79)	57.1% (16/28)
V/VI	14.3% (3/21)	14.3% (1/7)
Age		
<30 years	28.6% (2/7)	0% (0/1)
30-50 years	35.1% (20/57)	41.2% (7/17)
51-65 years	40.9% (36/88)	51.5% (17/33)
>65 years	50.0% (8/16)	40.0% (2/5)
Median Volume		
<Median Volume (2.6 mL)	31.7% (26/82)	34.6% (9/26)
≥Median Volume (2.6 mL)	46.5% (40/86)	56.7% (17/30)

	JUVÉDERM VOLBELLA® XC n/N (%)	Control n/N (%)
Investigational Site		
Site 10001	26.7% (4/15)	66.7% (4/6)
Site 10002	22.2% (2/9)	25.0% (1/4)
Site 10003	42.9% (3/7)	50.0% (1/2)
Site 10004	35.3% (6/17)	40.0% (2/5)
Site 10005	30.8% (4/13)	0.0% (0/2)
Site 10006	9.1% (1/11)	0.0% (0/1)
Site 10007	70.6% (12/17)	83.3% (5/6)
Site 10008	46.7% (7/15)	50.0% (2/4)
Site 10009	54.5% (6/11)	71.4% (5/7)
Site 10010	78.6% (11/14)	50.0% (2/4)
Site 10012	54.5% (6/11)	25.0% (1/4)
Site 10013	4.5% (1/22)	20.0% (2/10)
Site 10014	50.0% (3/6)	100.0% (1/1)

2. Effectiveness Results

The analysis of effectiveness was based on the 224 evaluable patients at the 3-month time point. Key effectiveness outcomes are presented in Tables 14 to 15.

Primary Endpoint

The primary analysis was to evaluate the non-inferiority (non-inferiority margin = 0.5 points) of Juvéderm VOLBELLA® XC to control. The primary effectiveness endpoint was the mean change in overall lip fullness from baseline to month 3 based on the Evaluating Investigator's assessments of overall lip fullness using the validated Allergan Lip Fullness Scale 2 (LFS2). The primary endpoint of the study was met with non-inferiority of Juvéderm VOLBELLA® XC to control. The mean change from baseline to month 3 on the LFS2 score was 1.1 for subjects treated with JUVÉDERM VOLBELLA® XC and 1.0 for subjects treated with control, with 80.3% (122/152) of subjects treated with JUVÉDERM VOLBELLA® XC and 70.8% (34/48) of subjects treated with control showing a ≥ 1 point improvement in overall lip fullness (Table 14).

Table 14: Primary Effectiveness Endpoint: Change from Baseline to Month 3 in Overall Lip Fullness (LFS2) Score (Modified Intent-to-treat Population)

	JUVÉDERM VOLBELLA[®] XC (N = 165)	Control (N = 53)	P-value	Difference (Lower Limit of 95% Confidence Interval)
N	152	48		
Mean	1.1	1.0	0.609	0.07
SD	0.75	0.85		(-0.15)
Median	1.0	1.0		
Min, Max	0, 4	0, 3		
95% CI	(0.9, 1.2)	(0.8, 1.2)		
P-value	< 0.001	< 0.001		

Throughout the follow-up period, JUVÉDERM VOLBELLA[®] XC continued to provide a clinically significant improvement in lip fullness (≥ 1 -point mean improvement on the LFS2 scale), with a majority of subjects treated with JUVÉDERM VOLBELLA[®] XC demonstrating improvement through 1 year (Table 15).

Table 15: Effectiveness Results Beyond Primary Endpoint

	JUVÉDERM VOLBELLA[®] XC
	% (n/N)
6 Months	71.1% (106/149)
9 Months	65.1% (95/146)
1 Year	61.8% (76/123)

Secondary Endpoints

Secondary measures included Evaluating Investigators' assessment of subjects' perioral lines using the validated perioral lines severity scale (POLSS) and subjects' satisfaction with their lips using the validated Satisfaction with Lips module of the FACE-Q questionnaire.

At 3 months, 65.4% (53/81) of subjects treated with JUVÉDERM VOLBELLA[®] XC showed a ≥ 1 point improvement in POLSS scores from baseline at rest. At 1 year, 66.2% (45/68) of subjects treated with JUVÉDERM VOLBELLA[®] XC maintained improvement in perioral lines severity at rest.

At 3 months, 96.1% (147/153) of subjects treated with JUVÉDERM VOLBELLA[®] XC reported improvement in satisfaction with their lips, based on the Satisfaction with Lips module of the FACE-Q questionnaire, with the mean score increasing from 38.5 at baseline to 76.5. At 1 year, 79.7%

(98/123) of subjects reported improved satisfaction with their lips over baseline, with a mean score of 59.6.

Other Effectiveness Assessments

Additional effectiveness measures included Evaluating Investigators' assessment of subjects' upper and lower lip fullness using the LFS2, oral commissures severity using the oral commissures severity scale (OCSS), global aesthetic improvement using the global aesthetic improvement scale (GAIS), and Satisfaction with Lip Lines module of the FACE-Q.

Improvements in upper and lower lip fullness were similar to the improvements seen in overall lip fullness through 1 year. Subjects treated with JUVÉDERM VOLBELLA[®] XC in the perioral lines and oral commissures also saw improvement in perioral lines severity at maximal contraction and oral commissures severity through 1 year.

On the GAIS at 3 months, 92.9% (143/154) of subjects in the JUVÉDERM VOLBELLA[®] XC group were scored as "improved" or "much improved" in appearance. At 1 year, the percentage of subjects "improved" or "much improved" was 58.5% (72/123) in the JUVÉDERM VOLBELLA[®] XC group.

At 3 months, subjects treated with JUVÉDERM VOLBELLA[®] XC reported a mean score improved to 72.9 from 37.5 at baseline on the Lip Lines module of the FACE-Q. The mean score was 56.3 in the JUVÉDERM VOLBELLA[®] XC group at 1 year.

Within the JUVÉDERM VOLBELLA[®] XC randomization group, repeat treatment with JUVÉDERM VOLBELLA[®] XC was administered to 124 subjects. The effectiveness profile after repeat treatment was similar to that after initial treatment, with 94.3% (115/122) of subjects showing at least a 1-point improvement in lip fullness, based on the Evaluating Investigator assessment at 1 month after repeat treatment.

3. Subgroup Analyses

Subgroup analyses of the primary effectiveness endpoint were performed by gender, age group, baseline overall LFS2 score, Fitzpatrick skin phototype (I/II, III/IV, and V/VI), volume injected (< or ≥ the median total injected volume of 2.6 mL), and investigational site. Similar results were observed in the JUVÉDERM VOLBELLA[®] XC and control groups within each subgroup (Table 16). Some subgroups (e.g., investigational sites, males, subjects < 30 years of age) had a small number of subjects, such that the analysis cannot support conclusions for those subgroups.

Table 16: Subgroup Effectiveness Analyses – Mean (\pm Standard Deviation) Change from Baseline in Overall Lip Fullness at Month 3 (mITT Population)

	JUVÉDERM VOLBELLA® XC (N = 168)		Control (N = 56)	
Subgroup	Subgroup N	Result	Subgroup N	Result
Baseline overall LFS2 score				
Minimal	32	1.7 (0.97)	10	1.8 (0.79)
Mild	65	1.0 (0.61)	25	1.0 (0.73)
Moderate	55	0.8 (0.54)	13	0.3 (0.48)
Volume injected at initial and touch-up treatment combined				
< median (2.6 mL ^a)	72	0.8 (0.60)	20	0.7 (0.81)
\geq median (2.6 mL ^a)	80	1.3 (0.80)	28	1.3 (0.80)
Fitzpatrick skin phototype				
I/II	67	1.1 (0.88)	18	1.0 (0.91)
III/IV	71	1.1 (0.66)	26	1.0 (0.87)
V/VI	14	0.8 (0.43)	4	0.8 (0.50)
Gender				
Male	2	0.5 (0.71)	2	0.5 (0.71)
Female	150	1.1 (0.75)	46	1.0 (0.86)
Age Group				
< 30 years	4	1.3 (0.50)	0	N/A
30 to 50 years	53	0.9 (0.68)	13	0.7 (0.75)
51 to 65 years	81	1.1 (0.74)	30	1.2 (0.91)
> 65 years	14	1.4 (1.02)	5	0.8 (0.45)
Investigational site				
10001	15	1.5 (0.52)	4	1.8 (0.50)
10002	8	0.6 (0.52)	3	1.0 (0.00)
10003	7	0.9 (0.38)	2	0.0 (0.00)
10004	15	0.3 (0.46)	5	0.4 (0.55)
10005	13	0.9 (0.28)	2	0.0 (0.00)
10006	8	1.0 (0.76)	1	1.0 (N/A)
10007	15	0.8 (0.41)	5	0.8 (0.45)
10008	15	0.7 (0.59)	4	0.5 (0.58)
10009	11	1.6 (0.81)	7	2.0 (0.82)
10010	14	2.1 (0.83)	3	1.7 (1.15)
10012	11	1.0 (0.45)	4	0.5 (0.58)
10013	14	1.3 (0.91)	7	0.9 (0.69)
10014	6	1.0 (0.00)	1	2.0 (N/A)

^a The median total volume injected across all injection sites at the initial and touch-up treatments combined

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 26 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

European Clinical Study

In this prospective, randomized, multicenter study, 280 subjects desiring lip volume enhancement were treated with JUVEDERM VOLBELLA[®] XC or RESTYLANE-L[®]. The subjects returned to the investigational sites at quarterly intervals for follow-up evaluations with the Treating Investigator. Subjects could receive repeat treatment with JUVEDERM VOLBELLA[®] XC at months 6, 9, or 12 if the investigator determined that the subject's LFS2 score had returned to baseline, or at month 12 if the subject's LFS2 score was lower than the treatment goal as assessed by the investigator. At 1 month after repeat treatment, subjects returned for a final follow-up visit and were then exited from the study.

Common and expected ISRs were collected via 30-day diaries after each treatment. The incidence, severity, and duration of ISRs for subjects treated with JUVEDERM VOLBELLA[®] XC after initial treatment are shown in Table 17. Most subjects reported an ISR after treatment, with the most common being swelling, tenderness, and firmness. The majority of ISRs were mild to moderate in severity and resolved within 14 days. The incidence of ISRs after touch-up treatment was lower than that after initial treatment. The ISRs after repeat treatment were similar to those after initial treatment.

Table 17: Injection Site Responses by Severity and Duration Occurring in > 5% of Treated Subjects after Initial Treatment^a with JUVÉDERM VOLBELLA[®] XC

ISR	Incidence (n/N ^b)	Severity ^c			Duration ^d			
		Mild	Moderate	Severe	1-3 Days	4-7 Days	8-14 Days	15-30 Days
Any ISR	95.5% (126/132)	17.5%	50.0%	32.5%	23.8%	28.6%	26.2%	21.4%
Swelling	90.9% (120/132)	31.7%	46.7%	21.7%	52.5%	40.8%	5.8%	0.8%
Tenderness	87.1% (115/132)	49.6%	42.6%	7.8%	57.4%	27.8%	10.4%	4.3%
Firmness	82.6% (109/132)	46.8%	38.5%	14.7%	45.9%	24.8%	18.3%	11.0%
Bruising	78.0% (103/132)	35.9%	41.7%	22.3%	35.0%	48.5%	15.5%	1.0%
Lumps/Bumps	76.5% (101/132)	37.6%	49.5%	12.9%	35.6%	25.7%	17.8%	20.8%
Redness	76.5% (101/132)	54.5%	38.6%	6.9%	73.3%	19.8%	6.9%	0%
Pain	68.9% (91/132)	50.5%	44.0%	5.5%	80.2%	16.5%	3.3%	0%
Itching	21.2% (28/132)	64.3%	25.0%	10.7%	82.1%	14.3%	3.6%	0%
Discoloration	17.4% (23/132)	65.2%	30.4%	4.3%	73.9%	21.7%	0%	4.3%

^a Does not include data after touch-up treatment

^b N denotes the number of subjects who recorded in the diaries after initial treatment

^c Maximum severity reported in the diary. Denominator for percentages by severity is the number of subjects with corresponding ISR

^d Maximum reported successive occurrence of an ISR. Denominator for percentages by duration is the number of subjects with corresponding ISR

ISRs lasting beyond the 30-day diaries were considered AEs. AEs were also reported by the Evaluating Investigator at follow-up visits. Among the 139 subjects treated with JUVÉDERM VOLBELLA[®] XC at the initial treatment, 14 (10.1%) experienced 22 treatment-related AEs before repeat treatment. The most common treatment-related AE was injection site mass (lumps/bumps). Subjects treated with JUVÉDERM VOLBELLA[®] XC experienced mild (7.9%, 11/139) or moderate (2.9%, 4/139) treatment-related AEs. In general, the treatment-related AEs required no action and resolved without sequelae.

Among the 139 subjects who were treated with JUVÉDERM VOLBELLA[®] XC at initial treatment and received repeat treatment with JUVÉDERM VOLBELLA[®] XC, 3 experienced 4 treatment-related AEs after repeat treatment. These AEs include 3 reports of injection site mass and 1 report of oral herpes. Of the 4 AEs, 2 were mild (1 injection site mass [lumps/bumps] and 1 oral herpes) and 2 were severe (both events were injection site mass [lumps/bumps] in 1 subject). The 2 mild AEs resolved without sequelae. At the end of the study, the 2 severe AEs of injection site mass (lumps/bumps) occurring in 1 subject had not yet resolved.

Among the 141 subjects who were treated with RESTYLANE-L[®] at initial treatment and received repeat treatment with JUVÉDERM VOLBELLA[®] XC, 4 experienced 8 treatment-related AEs after repeat treatment. These AEs include 6 reports of injection site induration (firmness), 1 report of injection site mass (lumps/bumps), and 1 report of oral paresthesia. Of these 8 AEs, 6 were mild (4 reports of injection site induration [firmness], injection site mass [lumps/bumps], and oral paresthesia), 1 was moderate (injection site induration [firmness]), and 1 was severe (injection site induration [firmness]). All of these treatment-related AEs required no action and resolved without sequelae.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of the U.S. pivotal study. These submitted data provided a reasonable assurance that the device is effective for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21. The specific conclusions are:

- The primary analysis was to evaluate the non-inferiority (non-inferiority margin = 0.5 points) of Juvéderm VOLBELLA[®] XC to control. The primary effectiveness endpoint was the mean change in overall lip fullness from baseline to month 3 based on the Evaluating Investigator's assessments of overall lip fullness using the validated Allergan Lip Fullness Scale 2 (LFS2). The primary endpoint of the study was met with non-inferiority of Juvéderm VOLBELLA[®] XC to control. The mean change from baseline to month 3 on the LFS2 score was 1.1 for subjects treated with JUVÉDERM VOLBELLA[®] XC and 1.0 for subjects treated with control, with 80.3% (122/152) of subjects treated with JUVÉDERM VOLBELLA[®] XC and 70.8% (34/48) of subjects treated with control showing a \geq 1 point improvement in overall lip fullness.
- Throughout the follow-up period, JUVÉDERM VOLBELLA[®] XC continued to provide a clinically significant improvement in lip fullness (\geq 1-point mean improvement on the LFS2 scale), with 61.8% subjects treated with JUVÉDERM VOLBELLA[®] XC demonstrating improvement through 1 year.
- At 3 months, 65.4% (53/81) of subjects treated with JUVÉDERM VOLBELLA[®] XC showed a \geq 1 point improvement in POLSS scores from baseline at rest. At 1

year, 66.2% (45/68) of subjects treated with JUVÉDERM VOLBELLA[®] XC maintained improvement in perioral lines severity at rest.

- At 3 months, subjects treated with JUVÉDERM VOLBELLA[®] XC reported a mean score improved to 76.5 points from the baseline score of 38.5 points on the Satisfaction with Lips module of the FACE-Q. The mean score at 1 year was 59.6 points in the JUVÉDERM VOLBELLA[®] XC group.
- The effectiveness profile after repeat treatment was similar to that after initial treatment, with 94.3% (115/122) of subjects showing at least a 1-point improvement in lip fullness, based on the Evaluating Investigator assessment at 1 month after repeat treatment.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in the clinical study conducted to support PMA approval as described above. The submitted data provide a reasonable assurance of safety of JUVÉDERM VOLBELLA[®] XC for lip augmentation and for correction of perioral rhytids in adults over the age of 21. The specific conclusions are:

- Almost all subjects (97.4%, 150/154 after initial treatment and 90.2%, 111/123 after repeat treatment) treated with Juvéderm VOLBELLA[®] XC reported at least 1 ISR. The most frequently reported ISRs after initial and repeat treatment were swelling, tenderness, firmness, bruising, lumps/bumps, redness and pain. Subjects reported the severity of their ISR after initial treatment as mild (14.7%, 22/150), moderate (45.3%, 68/150), or severe (40.0%, 60/150).
- Most ISRs lasted less than 2 weeks after initial (59.3%, 89/150) and repeat treatment (73.9%, 82/111), but 40.7% of the ISR lasted between 15-30 days of duration. The most common ISRs that lasted for 15 to 30 days after initial treatment were lumps/bumps (33.3%, 45/135), Dryness (25.0%, 2/8) and firmness (15.3%, 21/137). Similarly after repeat treatment, the most common ISRs lasting 15 to 30 days were lumps/bumps (22.4%, 22/98), firmness (13.1%, 13/99), and tenderness (3.9%, 4/103).
- In the time between initial treatment and before repeat treatment, 104 subjects (61.9%, 104/168) in the treated mITT population with VOLBELLA[®] XC treatment experienced 426 adverse events (treatment emergent adverse event, TEAE).
- After initial treatment, treatment-related adverse events were reported in 50.0% (84/168) of subjects treated with Juvéderm VOLBELLA[®] XC. Most subjects treated with Juvéderm VOLBELLA[®] XC experienced mild (42.3%, 71/168) or moderate (17.3%, 29/168) treatment-related AEs, only 1.2% (2/168) of subjects experienced severe treatment-related AEs. The treatment-related AEs generally required no action to be taken and resolved without sequelae (98.8%, 83/84).

- Similar types of treatment-related AEs were reported after repeat treatment, but with a lower incidence rate (13.7%, [17/124]), severity, and duration compared to initial/touch-up treatment.
- There were no deaths or treatment-related serious adverse events (SAEs) reported in the study.
- Similar proportions of ISRs and AEs were observed between VOLBELLA[®] XC group and the control groups for the following subgroup analysis: volume injected (< or ≥ the median injected volume of 2.6 mL), Fitzpatrick skin phototype (grouped as I/II, III/IV, and V/VI), age group (< 30, 30 to 50, 51 to 65, and > 65 years), and investigational site.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The study was a prospective, controlled study using a validated scale and blinded, live evaluations. The study investigated the safety and effectiveness of JUVÉDERM VOLBELLA[®] XC for lip augmentation and correction of perioral rhytids. The primary effectiveness endpoint was the analysis of non-inferiority of JUVÉDERM VOLBELLA[®] XC relative to control treatment in terms of change from baseline to month 3 in mean lip fullness based on Evaluating Investigator assessments using the 5-Point Lip Fullness Scale 2 (LFS2). The data are considered to be as robust as possible for an aesthetic endpoint. The primary endpoint of the study was met with non-inferiority of Juvéderm VOLBELLA[®] XC to control. Summary of effectiveness conclusions is provided above.

Additional factors to be considered in determining probable risks and benefits of JUVÉDERM VOLBELLA[®] XC injection included: Nearly all subjects (97.4%, 150/154 after initial treatment and 90.2%, 111/123 after repeat treatment) experienced an injection site response. Summary of safety conclusions is provided above.

The probable benefits outweigh the probable risks, as determined by the robustness of the effectiveness results, the lack of any long term sequelae, and the improvement of subject satisfaction on the FACE-Q questionnaires. The risks of short term adverse outcomes seen after injection and rare adverse events are sufficiently well understood for patients to make informed decisions about device use.

Patient Perspectives

Patient perspectives considered during the review included:

- Despite the frequency of ISRs, patients are willing to accept the probable risk of these harmful events as shown through patient-reported outcomes.
- At 3 months, 96.1% (147/153) of subjects treated with JUVÉDERM VOLBELLA[®] XC reported improvement in satisfaction with their lips, based on the Satisfaction

with Lips module of the FACE-Q questionnaire, with the mean score increasing from 38.5 at baseline to 76.5. At 1 year, 79.7% (98/123) of subjects reported improved satisfaction with their lips over baseline, with a mean score of 59.6.

- At 3 months, subjects treated with JUVÉDERM VOLBELLA[®] XC reported a mean score improved to 72.9 from 37.5 at baseline on the Lip Lines module of the FACE-Q. The mean score was 56.3 in the JUVÉDERM VOLBELLA[®] XC group at 1 year.
- In the JUVÉDERM VOLBELLA[®] XC group, 124 subjects received repeat treatment and 20 subjects refused repeat treatment at 12 months. The most common reason given for refusal of repeat treatment was satisfaction with current lip fullness. No subjects refused repeat treatment because of the occurrence of AEs or ISRs.

In conclusion, given the available information above, the data support the use of JUVÉDERM VOLBELLA[®] XC for injection into the lips for lip augmentation and for correction of perioral rhytids in adults over the age of 21, and the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on 5/31/2016.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: None